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The Epidemiology of Esophageal Adenocarcinoma

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Title: The Epidemiology of Esophageal Adenocarcinoma

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Abbreviations: BMI: Body mass index; CI: Confidence intervals; EAC: Esophageal adenocarcinoma; GERD: Gastroesophageal reflux disease; GWAS: Genome-wide association studies; HR: Hazard ratios; NSAID: Non-steroidal anti-inflammatory drugs; OR: Odds ratios; PPI: Proton pump inhibitors; SNPs: Single nucleotide polymorphisms.

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Abstract

The incidence of esophageal adenocarcinoma (EAC) has increased in many Western countries, and is higher in men than women. Some risk factors for EAC have been identified—mainly gastroesophageal reflux disease (GERD), Barrett’s esophagus, obesity, and tobacco smoking. It is not clear whether interventions to address these factors can reduce risk of EAC, although some evidence exists for smoking cessation. Although consumption of alcohol is not associated with EAC risk, other exposures, such as physical activity, nutrition, and medication use, require further study. Genetic variants have been associated with risk for EAC, but their overall contribution is low. Studies are needed to investigate associations between risk factors and the molecular subtypes of EAC. The prognosis for patients with EAC has slightly improved, but remains poor—screening and surveillance trials of high-risk individuals are needed.

Keywords: Epidemiology; Lifestyle; Genetic risk; Esophageal cancer

Esophageal adenocarcinoma (EAC) is characterized by several epidemiologic features. Over the past 30 years, there has been a rapid increase in the incidence of EAC in many Western countries, including Europe, North America, and Australia—EAC is the most rapidly increasing form of cancer in some populations.^{1,2} The male predominance in incidence is stronger than that of any other non–sex-specific cancer in several populations.^{2,3} Although strong risk factors for EAC have been identified, mainly gastroesophageal reflux disease (GERD) and obesity, we are in need of evidence-based preventive strategies.^{2,4} The prognosis for patients diagnosed with EAC has slightly improved during the last few decades, but it is still worse than that of most other cancer types; only 20% of patients in Western populations survive for 5 years.^{5–7} This review summarizes the current knowledge in the epidemiology and prevention of EAC, and highlights unresolved research questions regarding these topics.

Incidence

EAC is the main histological type of esophageal cancer in the West. In 2012, an estimated 52,000 individuals (41,000 men and 11,000 women) developed EAC worldwide, resulting in a global incidence rate of 0.7 per 100,000 person-years (1.1 in men and 0.3 in women); most patients (53%) were from Europe, Northern America, or Oceania.⁸ The incidence rate of EAC has surpassed that of esophageal squamous cell carcinoma in a number of Western countries, including the United Kingdom (UK), the Netherlands, Ireland, New Zealand, the United States (US), Australia, Denmark, Canada, and Sweden.^{8–11}

Geographic and racial/ethnic variations

The incidence rate of EAC varies greatly across geographic regions. The age-standardized incidence rate of EAC in 2012 was highest in Northern and Western Europe, Northern America, and Oceania, but was as low as less than 1 per 100,000 person-years in both sexes in the remaining parts of the world.⁸ At the individual country level, the highest rates per 100,000 person-years have been observed in the UK (7.2 in men and 2.5 in women), the Netherlands (7.1 in men and 2.8 in women), and Ireland (3.9 in men and 2.7 in women).⁸ In the US, the incidence rates are highest in non-Hispanic whites, followed by Hispanic whites, American Indian/Alaska Native, blacks, and lowest in Asian/Pacific islanders.^{12,13}

Time trends

Figure 1 shows the incidence trends of EAC since the 1970s in White Americans and in Sweden. The increase in the incidence of EAC seems to have started in the 1970s in Europe, North America, and Australia.¹ Some reports have suggested that EAC incidence might have reached a plateau in recent years,^{14,15} whereas other studies found a continued increase.^{1,10} A comprehensive assessment based on data from 8 Western countries, including incidence rates through the year 2009, indicated a continuing increase at seemingly unchanged rates; these ranged from an average 3.5% per year in Scotland to 8.1% per year in Hawaii.¹ The most recent update of EAC incidence, with data from Sweden through the year 2014, reported a continued increase, although the increase seemed to have slowed down to 2.6% per year in men from year 2000 onwards.¹⁶ A simulation model of the EAC incidence in the US estimates that incidence will continue to increase until 2013, but plateau for recent birth cohorts in men.¹⁷ The incidence of EAC has remained much lower in Asian populations, although a trend towards a increase has been noted in a few Asian countries, including Singapore and Israel.^{18–20} Time trends in EAC incidence should be monitored in different populations worldwide.

Age and sex distribution

EAC incidence increases with age,^{10,21} similar to the age-specific incidence patterns of most epithelial cancers. EAC is characterized by a striking male predominance in incidence—the excess risk in men is greatest in the US, where the male:female incidence ratio of as high as 9:1.^{3,8,22} A recent assessment of the sex-specific incidence rates in continents reported that ratios of incidence in men:women are also high in Northern America (7.6), Oceania (6.2), and Europe (6.0); ratios are lower in Asia (4.4), Latin America and the Caribbean (3.9), and Africa (1.0). The sex ratio has remained relatively stable over time in most populations, but has steadily increased in the UK and the Netherlands.²²

Genetic Factors

Technical innovations and increasing affordability of large-scale genetic studies have led to the identification of germline (inherited) variants that affect risk for EAC. Somatic variants (not inherited) that affect risk of EAC are covered in a separate article in this issue, by Graham et al.²³

Approximately 7% of cases of Barrett's esophagus (BE) or EAC occur within families.²⁴⁻²⁶ Familial cases develop at an earlier age than sporadic EACs.^{27,28} Other risk factors for EAC, such as regurgitation, smoking and obesity, are less prevalent among individuals with familial BE or EAC.²⁷ However, these findings might have been affected by participant and reporting biases, due to comparisons with family controls.

In 2016, researchers identified a germline mutation associated with a subset of EAC cases. A whole-exome sequencing study of a multi-generational family, in which 14 members were affected by BE or EAC, identified a variant in the V-set and immunoglobulin domain containing 10 like gene (*VSIG10L*), encoding S631G, as a possible cause of familial EAC.²⁹ The identification of this mutation provides opportunities for screening and surveillance of individuals with family members affected by BE or EA, depending on its prevalence. In future, the mutation could be incorporated into a risk prediction model, such as the BE Translational Research Network model, which combines family history and clinical risk factors to identify individuals at high risk for BE.³⁰

Candidate gene studies

Many candidate genes have been evaluated in relation to EAC and BE risk. A systematic review identified 31 studies reporting on 187 different candidate germline mutations and risk of these lesions.³¹ Few had been investigated in more than 1 study, many had methodologic flaws, so the ability to conduct meta-analyses has been limited. A variant in only the glutathione S-transferase pi 1 gene (*GSTP1*) (rs1695) was consistently associated with BE, with the 'G' allele increasing risk of BE by 50%.³¹ Variants in genes encoding several growth factors and interleukins, and in caudal type homeobox 1 (*CDX1*), were also associated with risk and encoded proteins with plausible involvement in carcinogenesis.³¹ Germline variants in genes that regulate inflammation,³² androgen signaling,³³ and cancer-related processes³⁴⁻³⁶ (such as apoptosis and angiogenesis, or in oncogenes or tumor suppressor genes) have also been investigated for their association with risk of EAC.

Genome-wide association studies (GWAS)

GWAS for BE and EAC risk have been reported from various consortia since 2012.^{37–39} These have identified a number of single nucleotide polymorphisms (SNPs) associated with risk (associated with loci at or close to the *MHC region*, *FOXF1*, *GDF7*, *TBX5*, *FOXP1*, *CRTC1*, *BARX1* and *ALDH1A2* genes).^{37–39} Many of these associations have been replicated in subsequent studies.^{40,41} One of the largest initiatives has pooled analyses of all GWAS studies published until February 2016, comprising 6167 cases of BE, 4112 cases of EAC, and 17,159 controls.⁴² These confirmed associations for all 8 previously identified SNPs, along with 8 new risk loci; 2 of these are linked to genes that regulate body fat.⁴² One variant (rs9823696, near *ABCC5* and *HTR3C*) was associated with EAC risk independently of BE, so it might be used to identify patients with BE at high risk for EAC.⁴²

Mendelian randomization studies are useful for studying genetic variants as instrumental variables, or proxies, for modifiable factors. They overcome issues of confounding, because the inheritance of alleles from each parent should occur randomly. This approach has been used to confirm associations between body composition measures and EAC risk (for example 30%–43% reduced risks of EAC per 10 cm increase in height, and 16% increased EAC risk per 1 kg/m² increment in body mass index (BMI)).^{43,44}

Genetic factors associated with EAC and clinical utility

Up to one third of EAC may be hereditary and attributed to a combination of germline mutations,⁴⁵ although single mutations are associated with only a 20% increase in risk of EAC, at most.²⁶ However, the sharp increase in EAC incidence in many countries cannot be accounted for by changes in the population's genetic make-up over a timeframe of only 50 years. Genetic predisposition might account for some of the variation in geographical incidence of EAC. For example, variants in the cystic fibrosis transmembrane conductance regulator gene (*CFTR*) associated with EAC in a GWAS are also associated with cystic fibrosis, which can be associated with reflux symptoms.⁴² Both diseases have a high incidence in the UK and Ireland;^{8,46} it is possible this variant is more common in people of Celtic descent.

The clinical utility of understanding genetic variants associated with EAC risk is perhaps limited, given the common prevalence and relatively low risk of EAC associated with many of the SNP

variants identified.^{26,47} However, the contribution of genetic studies to the enhanced biological understanding of susceptibility to EAC should not be underestimated. It is important to study interactions between genetic and environmental factors that affect risk for EAC, as these might increase our understanding of temporal trends in EAC incidence. For example variants in *FOXP1* modify the association between GERD and risk of BE.⁴⁸ However, such studies would require large sample sizes that are pragmatically difficult to achieve.

Non-genetic Risk Factors

Gastroesophageal reflux disease

GERD was first established as a risk factor for EAC in the late 1990s,^{49,50} and confirmed in population-based studies.^{51–54} A pooled analysis of 5 population-based case–control studies indicated a strong association between heartburn or regurgitation, the 2 most common GERD symptoms, and EAC risk (see Figure 2).⁵¹ The risk of EAC in individuals with heartburn for at least 30 years was 6.2-fold higher than in individuals without heartburn.⁵¹ A recent analysis of same 5 studies, along with 3 additional studies, showed that the association was stronger in adults younger than 50 years compared with older age groups.⁵⁵

BE

BE, the precursor to EAC, is characterized by metaplastic changes in the esophageal lining, from normal squamous to a specialized columnar epithelium, in patients with chronic GERD. The tumor development process involves consecutive changes, from erosive esophagitis to non-dysplastic BE, low-grade dysplasia, high-grade dysplasia, adenocarcinoma in situ, and finally invasive adenocarcinoma.⁵⁶ Individuals with BE and long-term GERD and additional risk factors should be screened by upper endoscopy for dysplastic BE or early-stage, curable EAC.^{57,58} However, EACs are missed in a large proportion of patients with BE, in spite of the screening strategy, because approximately 40% do not report GERD symptoms.⁵⁹

Temporal trends of GERD and BE

The temporal trends of GERD are rarely assessed in longitudinal studies, although systematic reviews comparing GERD prevalence reported by population-based studies in different calendar periods have suggested an increase in GERD prevalence since the mid-1990s, particularly in

North America and East Asia.^{60,61} A population-based cohort study in Norway, of 29,610 individuals followed up for an average of 11 years, found a 47% increase of at least weekly reflux symptoms from the period 1995–1997 to the period 2006–2009.⁶² It is likely that the increasing prevalence of GERD contributed the increasing incidence of EAC—particularly for the increase in more recent years. An increasing incidence of BE, particularly in younger men, was reported from 2 population-based European studies.^{63,64}

Anti-reflux therapies

The cancer protective potential of anti-reflux therapies, such as acid-suppressing medications, particularly proton-pump inhibitors (PPIs), and anti-reflux surgery with fundoplication, has been evaluated in observational studies that produced inconsistent results.^{54,65–69} A meta-analysis of 5 cohort studies and 2 case-control studies associated a 70% decrease in risk of EAC or high-grade dysplasia with PPI use in patients with BE (adjusted odds ratio [aOR], 0.29).⁶⁸ However, a more recent meta-analysis of these 7 studies plus 2 additional population-based case–control studies found that the association was no longer statistically significant (unadjusted OR, 0.43); no association was found in an analysis restricted to 5 studies with higher scientific quality and adjustment for confounders (aOR, 0.95).⁶⁹ A recent systematic review and meta-analysis of 12 studies indicated that anti-reflux surgery might prevent EAC better than anti-reflux medication in patients with GERD (incidence rate ratio, 0.76), although it was not possible to make conclusions from this study, due to the limited sample size and possible bias and confounding in existing studies.⁶⁷ The ability of anti-reflux therapies to prevent EAC remains requires evaluation in large-scale studies with long follow-up periods and control for confounding factors.

Obesity

Increasing BMI has been consistently associated with increasing risk of EAC, in a seemingly linear exposure–response pattern.^{52,70–72} Interestingly, the association between childhood or adolescent BMI and EAC risk seems to be stronger than that of adulthood BMI.⁷³ The increasing prevalence of obesity in Western populations could partially account for the increasing incidence of EAC. However, the increasing incidence of EAC seems to have started before the start of the obesity epidemic.^{74–76} A quantitative assessment has shown that the increase in obesity

prevalence may account for only a limited part (6.5%) of the increase in EAC incidence in the US.⁷⁴

There are several potential mechanisms behind the association between obesity and EAC risk. A mechanical contribution might be gastric compression due to extensive intra-abdominal adipose tissue causing increased intra-gastric pressure and disruption of the gastroesophageal junction and the lower esophageal sphincter, which could lead to GERD.^{77–81} Obesity is a systemic disease that may increase EAC risk through inflammatory and metabolic alterations.⁸¹ Studies have indicated associations between serum leptin and insulin levels, as well as metabolic syndrome components, and an altered risk of BE.^{82–85}

A prospective cohort study of 392 patients with BE reported associations between increased levels of leptin and insulin and EAC risk, and an inverse association between high molecular-weight adiponectin and EAC.⁸⁶ A large prospective cohort study of 578,700 participants (Me-Can) associated an increased risk of EAC with the metabolic syndrome (hazard ratio, 1.56 per unit increase of the composite z-score).⁸⁷ One case–controls study associated the metabolic syndrome with EAC,⁸⁸ whereas 2 other case–control studies did not.^{89,90} Metabolic profiling studies using high-performance liquid chromatography–mass spectrometry or nuclear magnetic resonance analysis identified some metabolic markers in serum that might differentiate patients with EAC from healthy individuals or patients with BE.^{91,92} These findings require validation in independent populations.

Abdominal adiposity (typical male obesity) is associated with increased risk of EAC; this association seems to remain after adjustment for BMI.^{93,94} On the other hand, the association between BMI and EAC risk did not remain after adjustment for abdominal obesity.⁹³ A meta-analysis observed increased risk of BE associated with abdominal adiposity based on 11 studies, using patients with GERD as controls or adjusting for GERD symptoms, reported a reflux-independent effect of abdominal adiposity on development of esophageal metaplasia.⁹⁴ A prospective cohort study of 391,456 participants found an inverse association between gluteo-femoral adiposity (typical female obesity), measured by hip circumference. The adjusted hazard ratio of EAC was 0.35 when the highest vs the lowest quintile were compared, after controlling

for waist circumference.⁹⁵ These findings indicate a role for fat distribution in the male predominance in EAC. However, the male predominance seems to persist at a similar level even in lean individuals compared with overweight individuals.⁹⁶

Weight loss

Weight loss might reduce risk of EAC development, although this has been difficult to investigate. To study this effect, researchers would have to assess effects of exposure to substantial and consistent voluntary weight loss. It might be possible to study patients who have undergone obesity surgeries, but this would require large-scale investigations with long follow-up periods. A nationwide Swedish population-based cohort study of 34,437 patients who had undergone obesity surgery identified only 8 patients with EAC during a median of 3.7 years of follow up; it found no clear difference in EAC between individuals who underwent obesity surgery and 123,695 obese individuals who did not receive surgery (hazard ratio, 0.9).⁹⁷ It is therefore unclear whether weight loss is associated with a reduced risk of EAC.

Microbes

Infection with the gastric bacterium *Helicobacter pylori* has been associated with a decreased risk of EAC. Meta-analyses of observational studies have reported a 40%–60% reduced risk of EAC associated with *H pylori* infection.^{98–101} The prevalence of *H pylori* infection has decreased in Western populations since the middle of the 20th century, which was earlier than the start of the increasing incidence of EAC. So, the decreasing prevalence of *H pylori* infection may have contributed to the increasing EAC incidence in Western populations.^{76,102,103}

A possible mechanism of the inverse association between *H pylori* infection and EAC risk could include reduced volume and acidity of gastric juice, due to atrophic gastritis following *H pylori* infection, which in turn could counteract GERD and thereby reduce the risk of EAC.^{104,105}

However, 2 meta-analyses found no increased risk of GERD following *H pylori* eradication,^{106,107} although the association between *H pylori* eradication and EAC remains to be examined in epidemiological studies.^{4,108}

There have been few studies of the roles of bacteria other than *H pylori* in development of EAC. In a cultural analysis comparing esophageal biopsy specimens from 30 patients with EAC and 39 controls, more bacterial species were identified in the EAC samples (73 species from 23 genera) than in controls (56 species from 19 genera).¹⁰⁹ Evidence does not support an etiological role of infection with human papilloma virus in EAC.^{110–112}

The widespread introduction of antibiotics in the 1940s and the rapid increase in their use might have altered gastrointestinal microbiomes worldwide. Changes in species diversity or abundance of the esophageal microbiome might have contributed to the increasing incidence of EAC.^{76,113} However, it is not clear how the intestinal microbiome affects risk of EAC—further studies are needed. Next-generation sequencing technologies have enabled characterization of the gut microbiome with high resolution, with 16S ribosomal RNA gene amplicons and shotgun metagenomics approaches.¹¹⁴ These techniques will advance studies of the gastrointestinal microbiome on EAC development.

Tobacco smoking

Tobacco smoking is a well-established and moderately strong risk factor for EAC in men and women, with ever smoking conferring an approximately doubled risk of EAC compared with never smoking (OR, 1.96).¹¹⁵ Pooled analysis of 10 case–control and 2 cohort studies within the International Barrett's and Esophageal Adenocarcinoma Consortium (BEACON) consortium confirmed a dose-response association between pack-years of tobacco smoking and EAC risk, rising to a 2.7-fold increased risk for individuals who had 45 or more pack-years of smoking history.¹¹⁵ Further, the Northern Ireland Barrett's register reported an approximate 2-fold increased risk of progression from BE to EAC associated with tobacco smoking,¹¹⁶ a finding confirmed in subsequent smaller cohorts.^{117,118} Overall, it is plausible that tobacco smoking contributes to EAC development, given that tobacco is a carcinogen that causes DNA damage in Barrett's epithelium.¹¹⁹ A recent US study of 81 samples associated tobacco smoking with DNA hypermethylation in esophageal tissues.¹²⁰

Importantly from a public health perspective, smoking cessation appears to reduce this risk of EAC; individuals who have stopped smoking for 10 years or more have an approximate 30%

reduced risk of EAC compared with current smokers.¹¹⁵ However, a recent meta-analysis of 23 studies found only a small difference in the risk of EAC in comparing former and current smokers, and risk of EAC was reduced only among those who had stopped smoking for more than 20 years (risk ratio, 0.71).¹²¹ The risk of EAC in former smokers does not appear to return to the level observed in never-smokers,^{115,121} so primary prevention of smoking uptake in the population, particularly among children, should remain a priority.

Health service studies are needed to evaluate partnerships between gastroenterology and smoking cessation clinics within hospitals, as are targeted smoking interventions for patients with BE or reflux. Given that smoking relaxes the lower esophageal sphincter, thereby potentially increasing acid reflux exposure, studies evaluating different smoking cessation modalities¹²² in these patients are warranted for maximal risk reduction.

Alcohol consumption

Although alcohol is a recognised risk factor for the development of many cancers,^{123–125} this association does not apply to EAC etiology. Pooled analysis from the International BEACON consortium confirmed no association between alcohol intake and an increased risk of EAC, even in individuals consuming the highest levels of alcohol (7 or more drinks per day compared with non-drinkers; OR, 0.97).¹²⁶ The same pooled analysis, of 11 studies worldwide, found that moderate consumption of alcohol, and particularly wine, reduced EAC risk (0.5 to fewer than 1 drink per day compared with non-drinkers; OR, 0.63).¹²⁶

Similar results have been observed in analyses of alcohol and BE risk from 5 population-based case–control studies within the same consortium.¹²⁷ Further cohort studies have also reported no association between alcohol and the risk of progression from BE to EAC.^{116,128,129} These consistent findings contrast the strong, direct association between alcohol intake and esophageal squamous cell carcinoma risk.^{125,126} However, a 20% increase in risk of EAC was observed in individuals with alcohol-use disorders in a Swedish registry cohort study,¹³⁰ so these largely null associations for EAC may not apply to individuals who chronically abuse alcohol. Due to coding as alcohol misuse, rather than an estimate of alcohol consumption, this study may be limited in its ability to adjust for known confounders.

It is unclear why alcohol is a carcinogen in other tissues, it does not contribute to development of EAC. Methodological biases in study designs are unlikely to explain this inconsistency, because these are not unique to epidemiological studies of EA. It is possible that individuals with GERD may alter (likely reduce) their alcohol consumption. The association between alcohol use and reduced risk of EAC is limited to individuals without symptoms of acid reflux.¹³¹ Others have attributed the protective effects of alcohol on EAC risk to changes in insulin resistance, lipid metabolism, or the anti-oxidants present in some alcoholic drinks.¹²⁶ Further studies are required.

Dietary factors

Nutritional epidemiology is a particularly challenging field. It is a challenge to assess associations between disease outcomes and foods, nutrients, or composite dietary patterns or nutritional indices. The most comprehensive global report of diet, nutrition, and esophageal cancer, published in 2016, only considers evidence from cohort studies.¹²⁵ In this report, no dietary aspects were judged to have strong evidence of an association with EAC risk, whereas only vegetable intake had limited suggestive evidence for a relation to a reduced risk of EAC.¹²⁵

Because EAC is relatively rare, most studies of diet, nutrition, and EAC risk are of case–control design. Such studies are prone to recall and socially desirable respondent biases, which can cause measurement errors, or issues of reverse causation when they evaluate biomarkers of nutritional status. Nevertheless, they provide useful insights in the absence of cohort study evidence. A meta-analysis of 8 case-control studies found no protective effect of dietary fiber on EAC risk; individuals consuming the highest compared with the lowest intakes of dietary fiber had 34% reduced odds of EAC (pooled OR, 0.66).¹³²

Evaluating the strength and consistency of evidence for the spectrum of foods, nutrients, and related biomarkers across reflux esophagitis, BE and EAC risk within the same population can somewhat help to overcome some limitations of the case–control design. This was the premise for a population-based study in Ireland (see Table 2).^{133–141} Intake of vitamin C, magnesium, folate, vitamin B6, and non-heme iron were associated with reduced risks of esophagitis, BE, and

EAC. The findings were supported by the inverse associations between BE, EAC and intake of fruit and vegetables, toenail iron, and ferritin levels in this population.

Intake of dietary fat was consistently associated with increased risks of esophagitis, BE, and EAC. In contrast, several associations were made between only diet or nutritional exposures and EAC risk, indicating recall bias. Dietary fat was also associated with early stages of EAC development, in the inflammation–metaplasia–adenocarcinoma pathway. Overall, improvements in dietary assessment methods in population studies and large consortiums are needed to help strengthen the evidence for the associations between diet, nutrition, and EAC risk.

Physical activity and sedentary behavior

The 2016 World Cancer Research Fund/American Institute for Cancer Research continuous update project report on diet, nutrition, physical activity and esophageal cancer wrote that there is only “limited suggestive evidence” that physical activity reduces risk of EAC.¹²⁵ This was despite findings from 2 meta-analyses (published in 2014) that risk for EAC was reduced by 21%–32% in the most active vs the least active individuals.^{142,143} However, these pooled risk estimates were largely derived from case–control study estimates, which might be influenced by recall bias, whereas the associations observed in cohort studies were non-significant.^{144,145}

The Physical Activity Collaboration of the National Cancer Institute’s Cohort Consortium reported an association between self-reported physical activity and cancer risk in more than 1.44 million adults.¹⁴⁶ In their pooled analysis, high levels of physical activity associated with a reduced risk of EAC—more so than for any other cancer site (summary hazard ratio, 0.58, comprising 899 EAC cases from 5 studies). This inverse association remained after adjustment for BMI. However, in a stratified analysis, the protective effect was strongest for overweight and obese individuals, rather than healthy-weight individuals.¹⁴⁶

There is increasing recognition that sedentary behavior is distinct from physical activity level, and has adverse effects on health. There have been only a few studies of the effects of sedentary behavior and esophageal cancer risk—most reported no significant association.^{144,147,148} However, these were limited by inability to distinguish adenocarcinoma and squamous cell carcinoma

subtypes^{147,148} and small numbers of EAC cases.¹⁴⁴ In contrast, a National Institutes of Health–American Association of Retired Persons study reported a decreased risk of EAC in individuals who spent up to 6 hrs/day watching television (compared with less than 1 hr/day, adjusted hazard ratio, 0.57).¹⁴⁹

Overall, studies of physical activity, sedentary behavior and EAC risk to date have been hampered by lack of objective assessments of physical activity (such as accelerometers), and lack of understanding of the biological mechanisms involved. To our knowledge, only 1 trial has investigated exercise as a means for EAC prevention.¹⁵⁰ In this Australian feasibility trial, 33 men with BE underwent a 24-week moderate activity intervention. Results demonstrated a significant reduction in waist circumference, but not BMI or other obesity-related biomarkers investigated, although being a feasibility trial this was not powered to detect significant changes.¹⁵⁰ This trial was hampered by difficulties in recruitment and the authors suggest a combined dietary and activity intervention may be more successful.¹⁵⁰ Nevertheless, this study represents an important first step in the progression from observational epidemiology to lifestyle interventions in EAC risk reduction.

Hormone and reproductive factors

The strong male predominance in EAC led to investigations of whether sex hormones might be involved in the etiology of EAC. For example, estrogens might protect against esophageal cancer, or androgens might promote its development.³ A meta-analysis of 5 observational studies found a reduced risk of EAC in post-menopausal women who use menopause hormone therapy compared with non-users (pooled OR, 0.75), and a borderline significant decreased in risk associated with use of oral contraceptives (OR, 0.76).¹⁵¹ A Swedish cohort study confirmed the inverse association between menopause hormone therapy and EAC risk (OR, 0.62); the risk reduction was more pronounced in users less than 60 yrs old (OR, 0.20).¹⁵² However, confounding by indication might be a threat to the validity of these pharmaco-epidemiologic studies.

The statistical power in previous epidemiological studies examining associations between reproductive factors and EAC risk was limited by the low incidence of EAC in women.

Interestingly, a pooled analysis of 3 population-based case–control studies revealed a decreased EAC risk associated with increasing duration of breastfeeding (OR, 0.42 for more than 12 months).¹⁵³ Continued research efforts are required to establish a role of sex hormone exposures in the etiology of EAC and to determine mechanisms.³

Medications

There are strong inverse associations between use of non-steroidal anti-inflammatory drugs (NSAIDs) and statins and the risk of EAC. A pooled analysis of 6 population-based observational studies associated NSAIDs use with a 32% reduced risk of EAC (OR, 0.68).¹⁵⁴ A pooled analysis of 8 randomized clinical trials, in which EAC was not a primary endpoint of interest, comprising 25,570 patients, found a strongly reduced 20-year risk of death from EAC in daily aspirin users compared with non-users (hazard ratio, 0.36).¹⁵⁵ However, the use of NSAIDs to prevent EAC development requires careful consideration of the absolute risk of EAC in individual patients and negative effects of these medications.⁴

A meta-analysis of 3 cohort studies and 2 case–control studies associated use of statins with a 41% reduced risk of EAC in patients with BE (OR, 0.59).¹⁵⁶ A recent case–control study nested in a cohort of patients with BE associated statistically non-significant reduction in EAC risk with statin use during over 3 years (OR, 0.5).⁶⁶ The potential preventive effect of statins on EAC development should be confirmed in large randomized controlled trials.

Observational studies have revealed an increased risk of EAC associated long-term use of drugs that relax the lower esophageal sphincter—particularly anticholinergics, which might be explained by a decreased pressure of the lower esophageal sphincter contributing to long-standing gastroesophageal reflux.^{157–160}

Due to its estrogenic properties, digitalis medication has been proposed to influence the risk of sex hormone related cancers. A recent Swedish population-based cohort study of 156,385 digitalis users and a comparison group of 551,993 users of organic nitrates associated digitalis use for at least 2 years with reduced risk of EAC (hazard ratio 0.48). The anti-cancer properties

of digitalis are being investigated in early-phase clinical trials of patients with cancer.^{161,162} However, these trials might not be powered enough to assess EAC risk.

In summary, although some medications appear to reduce risk of EAC, there is insufficient evidence for their use in EAC prevention. If protective effects of these drugs are confirmed in large controlled trials with sufficient length of follow up, it might become appropriate to introduce chemoprevention to individuals with high absolute risk of EAC, such as older men with obesity and GERD or individuals with BE, after balancing potential comorbidities in each patient.⁴

Prognosis

Generally, the overall prognosis in EAC is poor. This is mainly due to the late presentation of symptoms and the aggressiveness of this tumor. Most patients present with distant disease or a primary tumor with overgrowth of adjacent organs, making them incurable.¹⁶³ There are few data on patient prognoses from many countries, but patients with esophageal have poor prognoses in most parts of the world, indicated by similar global rates of incidence and mortality.¹⁶⁴ However, population-based studies have shown increases in 5-year survival, from less than 5% in the 1960s to about 20% from year 2000 and later in some European countries, the US, and China.^{5-7,165} The most important prognostic factor is tumor stage, supporting the critical role for early detection for EAC. Rates of survival of patients with EAC vary with tumor stage in Northern Ireland (see Figure 3). Five-year survival rates decrease from 80.5% in the small proportion of EAC patients with stage I tumors, to 45.1%, 17.6% and 2.1% for patients with stage II, III and IV tumors, respectively.

In addition, the prognosis for patients who receive surgical therapy has improved.¹⁶⁶ Reasons for these improvements include earlier tumor detection due to higher general awareness and surveillance of individuals with BE, more accurate selection of patients for curative treatment, better surgical and perioperative therapy, and the addition of neoadjuvant chemotherapy or chemoradiotherapy for localized EAC.^{6,167-169} The tumor response to neoadjuvant chemotherapy or chemoradiotherapy is another important prognostic factor. Tumor stage at the time of surgery (pathological tumor stage) might be an even stronger prognostic factor than tumor stage at the

time of diagnosis (clinical tumor stage).¹⁷⁰ Other prognostic factors include patients' performance status, co-morbidities, and health-related quality of life.^{5,171}

Given the poor prognosis of patients with EAC, screening of certain high-risk individuals could be used to detect premalignant lesions (e.g. BE, dysplasia) or invasive EAC at a curable stage. However, endoscopic screening might not be cost-effective or feasible, so less-invasive methods such as Cytosponge or breath tests might be used.^{172,173} Screening and early detection of EAC is discussed in further detail in the accompanying article in this issue by di Pietro et al.¹⁷⁴

Future Directions

We have reviewed the epidemiological studies of EAC. It is important that future research builds upon current evidence. Important subjects for future research include:

- Continued evaluation of population trends in EAC incidence and prognosis, particularly in screening trials in high-risk population groups
- Efforts to improve earlier detection of EAC, to improve prognosis and treatment options
- Improved measurement of lifestyle exposures in epidemiological studies of EAC, for example through objective measures of physical activity and improved methods of dietary assessment
- Further interventional studies of anti-reflux therapies, weight loss, physical activity, and smoking cessation in individuals at risk of EAC
- Increasing our understanding of mechanisms of pathogenesis, and genetic and lifestyle factors that increase or decrease risk of EAC
- Improved understanding of the male predominance for EAC and associated biological mechanisms
- Identifying strategies for EAC prevention, and pharmaco-epidemiological studies to quantify the magnitude of associations between medications and EAC risk
- Increasing our understanding of bacteria and the gastrointestinal microbiome in EAC development
- Molecular pathology epidemiology studies to determine whether the association between modifiable risk factors and EAC differs with molecular subtype of tumor¹⁷⁵

Molecular pathology epidemiology studies have been successfully applied to studies of other cancers, most notably to colorectal cancer, to increase understanding of etiology and progression.^{176–178} Such studies require collection of epidemiological data and tissue from EAC patients to study associations between risk factors and molecular subtypes of EAC. These, and the other research directions, will require strong infrastructure and input from interdisciplinary research teams, and collaboration among research groups and consortia.

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Figure 1 legend: Incidence trends of esophageal adenocarcinoma in whites in the US, 1973–2014 (A) and the trends in Sweden, 1970-2015 (B). Data sources: Surveillance, Epidemiology, and End Results (SEER) Program, SEER*Stat Database: Incidence - SEER 9 Registries Research Data, Nov 2016 Submission; and the Swedish Cancer Registry.

Figure 2 legend: Forest plots of associations between heartburn and regurgitation exposures in relation to case and control groups in BEACON.⁵¹ (A) The association between recurrent heartburn or recurrent regurgitation in relation to esophageal adenocarcinoma. (B) The association between heartburn and regurgitation duration in relation to esophageal adenocarcinoma. (C): The association between heartburn and regurgitation frequency in relation to esophageal adenocarcinoma. D. The frequency of recurrent heartburn or recurrent regurgitation exposure in case and control groups by study. For each plot, each white square represents the study-specific odds ratio (A–C) or prevalence of exposure (D) and the black diamond represents the overall estimate. The arms of each symbol portray the 95% confidence intervals.

Figure 3 legend: Net survival by tumor stage of esophageal adenocarcinoma patients diagnosed in Northern Ireland, 2003-2010. Data sources: The Northern Ireland Cancer Registry. The total number of patients included in analysis by stage I, II, III, IV and unknown tumor type are 59, 95, 112, 185 and 288, respectively.

Table 1. Non-genetic risk factors for EAC

Factor	Direction of association	Strength of association	Type of studies conducted	Related notable findings	References
Gastroesophageal reflux disease	Positive	6.2-fold increased risk	Meta-analyses of population-based studies	The association was stronger in young adults (<50 years) than in older individuals.	51-55
Anti-reflux therapies	Inverse	Inconsistent	Meta-analyses of population-based studies	No association between proton-pump inhibitors use and EAC risk observed with adjustment for confounders; role of anti-reflux surgery in preventing EAC remains uncertain.	54,61-65
Obesity	Positive	Strong, linear dose-response association	Meta-analyses of population-based cohort studies	Abdominal adiposity has been associated with increased EAC risk after adjustment for body mass index.	52,70-77
Weight loss	Probably inverse	Uncertain	Interventions of obesity surgery	Existing evidence remains insufficient.	97
Tobacco smoking	Positive	2–3-fold increased risk.	Meta-analyses of population-based studies	Individuals who have stopped smoking for ten years or more having an approximate 30-40% reduced risk of EAC compared with current smokers.	115-118, 121
Alcohol	No association	No association	Meta-analyses of population-based	Potential inverse association for moderate consumption of alcohol, particularly wine.	126-131

			studies		
Dietary factors	Various	Various	Mostly case-control studies	Evidence is limited for a protective effect of vegetable intake and dietary fiber. Insufficient for all other factors.	125, 132-141
Physical activity	Inverse	30%–40% reduced risk	Cohort and case-control studies	Potential increased risks of EAC and sedentary behavior require further study.	125, 142-150
<i>Helicobacter pylori</i> infection	Inverse	40%–60% reduced risk	Meta-analyses of observational studies	Evidence for other infectious agents remains insufficient.	98-112
Menopausal hormone therapy and oral contraceptives	Inverse	25% reduced risk	Meta-analyses of population-based studies	Confounding by indication could not be ruled out in many studies.	151, 152
Breastfeeding	Inverse	58% reduced risk	Meta-analyses of population-based case-control studies	Decreased EAC risk associated with increasing duration of breastfeeding >1 year. Other reproductive factors require further study.	153
Non-steroidal anti-inflammatory drugs	Inverse	32%–64% reduced risk	Meta-analyses of population-based studies and Randomized controlled trials	Benefits of these medications for EAC prevention need to be carefully considered against potential harm due to known side effects.	154, 155
Statins	Inverse	41%	Meta-analyses of	Reduced EAC risk associated with statins use in patients	62, 156

reduced risk	population-based studies	with BE; the preventive effect of statins against EAC development remains to be confirmed in large randomized controlled trials.
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Table 2. Dietary factors, nutrient status, and risk of reflux esophagitis, BE, and EAC				
Dietary variable	Reflux esophagitis	BE	EAC	Reference
FOOD GROUPS				
Dairy products	-	+	+	Mulholland <i>et al</i> ¹³⁵
Fruit and vegetables		-	-	Anderson <i>et al</i> ¹⁴⁰
Total red meat	=	=	=	O’Doherty <i>et al</i> ¹³⁷
White meat	-	-	-	
Processed meat	++	+	+	
Total fish	+	+	+	
NUTRIENT INTAKES				
Total carbohydrate	=	=	--	Mulholland <i>et al</i> ¹³⁶
Glycemic index	+	=	++	
Glycemic load	=	=	=	
Dietary fiber	-	--	-	
Vitamin D	-	=	++	Mulholland <i>et al</i> ¹³⁵
Calcium	-	=	=	
Magnesium	--	--	--	Dai <i>et al</i> ¹³³
Folate	--	--	-	Sharp <i>et al</i> ¹³⁴
Vitamin B12	=	++	++	
Vitamin B6	--	--	--	
Vitamin C	--	-	--	Murphy <i>et al</i> ¹⁴¹
Vitamin E	-	-	=	
Zinc	-	-	+	
Copper	-	-	=	
Selenium	+	=	=	
Antioxidant index	+	=	--	
Heme iron		++	++	O’Doherty <i>et al</i> ¹³⁸

Non-heme iron		--	--	O'Doherty <i>et al</i> ¹³⁷
Total fat	++	+	++	
Saturated fat	++	=	++	
Monounsaturated fat	++	+	++	
Polyunsaturated fat	++	=	+	
NUTRIENT STATUS				
Serum iron		-		O'Doherty <i>et al</i> ¹³⁸
Ferritin		--		
Toenail iron		-	--	
Toenail Selenium		--	=	O'Rorke <i>et al</i> ¹³⁹
Toenail Zinc		++	=	

Notes: Data taken from the All Ireland Factors Influencing the Barrett's Adenocarcinoma Relationship study.

Table 2 Legend:

-- Significant inverse (protective) associations observed.

- Non-significant inverse (protective) associations observed.

= No significant associations observed.

+ Non-significant positive (increased risk) associations observed.

++ Significant positive (increased risk) associations observed.

Blank cells indicate that the association was not studied in that disease group.





